PITT STREET RESEARCH

Invion Limited

Helping cancer to see the light

Share Price: $0.015

Valuation range: A$ 0.031 – A$ 0.098

ASX: IVX

Sector: Pharmaceuticals

21 May 2019

Invion is a player in PhotoDynamic Therapy

Invion, which was formerly focused on the development of new drugs for respiratory disorders, in late 2017 changed direction with the acquisition of rights to a new Photodynamic Therapy (PDT) for the treatment of cancer. PDT, in which light-sensitive drugs are used to kill cancer cells, has been worked on by companies and academic groups for many years, but the approach has yet to mainstream as a cancer therapy. We argue that that is about to change, thanks to the recent European approval of a PDT called Tookad, initially indicated for localised prostate cancer. Invion's competing product, called IVX-P02 (previously Photosoft or NGPDT), has generated some interesting case studies and early clinical data, and the company will now proceed to conduct larger studies aimed at registration in Australia and New Zealand, possibly by 2021.

Lowered funding risk

The initial indication for IVX-P02 will be non-melanoma skin cancer, but there is potential in many other cancers including prostate, ovarian and lung cancers. Funding for the clinical work is being provided on a non-dilutionary basis through an R&D services agreement between Invion and Photosoft's original developer, the Guangzhou-based Cho Group, which (with associates) owns 66% of Invion. This provides significant upside for Invion's shareholders from Photosoft.

Investment case: A fast path to market

Invion expects to initiate Phase 1 studies in basal cell carcinoma and in mesothelioma in the third quarter of 2019. This puts the company on a path to be filing for its first Australian or New Zealand registration in 2021 for non-melanoma skin cancer and for mesothelioma possibly in 2023.

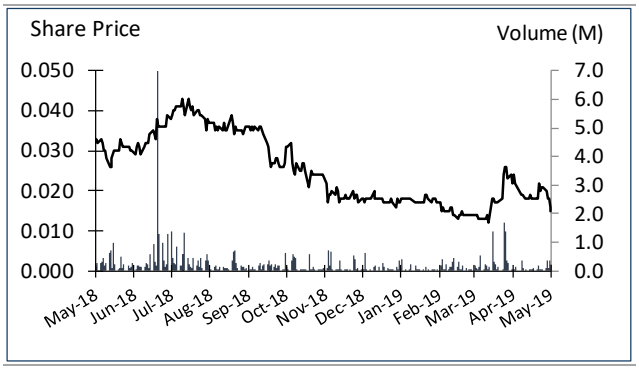
Valuation range of A$0.031 – A$0.098 per share

We value Invion at 3.1 cents per share base case and 9.8 cents optimistic case using a probability weighted DCF approach. Since listing investors have tended to afford Invion a generous market capitalisation. Invion stock has come back from the highs of 2018, but has potential to at least maintain the current share price and potentially re-rate again as the clinical development of IVX-P02 further de-risks this product.

Market Cap. (A$ m)	82.5
# shares outstanding (m)	5,500.6
# share fully diluted	5,865.3
Market Cap Ful. Dil. (A$ m)	88.0
Free Float	~34%
12 months high/low	0.048 / 0.012
1 / 3 / 12-month performance	38% / 6% / -55%
Website	inviongroup.com

Source: Company, Pitt Street Research

Share price (A$) and avg. daily volume (k, r.h.s.)



Source: FactSet, Pitt Street Research

Valuation metrics	
DCF fair valuation range (A$)	0.031 / 0.098
WACC	10.1%
Assumed terminal growth rate	3%

Source: Pitt Street Research

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Table of Contents

Introducing Invion

PDT is moving into the mainstream in cancer therapy

Invion is now a player in Photodynamic Therapy for the treatment of cancer. Invion (ASX: IVX), which was formerly focused on the development of new drugs for respiratory disorders, in late 2017 changed direction with the acquisition of rights to a new Photodynamic Therapy (PDT), initially for the treatment of localised prostate cancer, but with potential in many other cancers. Photodynamic Therapy (PDT) involves the use of light-sensitive compounds to kill abnormal cells. Under the NGPDT Transaction of 2017, which was announced to the ASX on 31 August 2017 and which was approved by shareholders on 30 November 2017, Invion acquired the exclusive commercialisation and distribution rights in Australia and New Zealand to a new PDT called NGPDT[1] for A$5.5m, satisfied through the issue of Invion shares[2]. As part of the NGPDT Transaction, the vendor and licensor of the product, the Guangzhou-based Cho Group, recapitalised Invion in early 2018 by fully underwriting a A$2.5m non-renounceable entitlement issue at 0.2 cents per share[3]. Invion then started the groundwork for clinical development of NGPDT, which the company initially called Photosoft, in Australia and New Zealand, aimed at local registration of a new formulation called IVX-P02. Invion will begin with non-melanoma skin cancers and then move on to solid tumours, since Invion's license covers the use of Photosoft in all cancers in the two countries. The first solid tumour indication will be mesothelioma. Encouragingly, non-dilutive funding for the various clinical studies will be provided by the Cho Group. After the 2018 rights issue the Cho Group held ~66% of Invion stock.

What is Photodynamic Therapy and how is it set to 'mainstream' in cancer therapy? In PDT, the patient is administered a drug called a 'photosensitising agent' that is preferentially taken up by cancer cells. When the patient is exposed to light beams at a wavelength corresponding to the 'absorption band' of the photosensitiser, the drug produces activated oxygen molecules that are toxic to nearby cancer cells. PDT has been worked on by companies and academic groups for many years, but the approach has yet to mainstream as a cancer therapy in part because the photosensitising agents that have been tried lacked either water solubility for good tissue distribution, strong absorption of long wavelengths allowing cancer to be reached at depth, or low circulation times so that patients weren't left vulnerable to damage from sunlight. One product that has all these qualities is a new PDT called Tookad, from a privately held company called Steba Biotech. We argue that Tookad's 2016 Phase 3 clinical success in prostate cancer, and November 2017 European approval, can be the product that moves PDT into the mainstream.

What is IVX-P02 and why does it represent a promising new cancer treatment approach? IVX-PO2, previously known as NGPDT and Photosoft, is Invion's lead molecule. NGPDT, short for 'Next Generation Photo Dynamic Therapy', is a photosensitising agent with similar qualities to Tookad, only with less clinical data than that which has been generated for Steba's product. Various case studies and early clinical studies have hinted at NGPDT's effectiveness in multiple cancers. IVX-P02 is Invion's reformulation of NGPDT/Photosoft. Invion will now seek to generate the validating clinical data

[1] Cho Group had previously sought to vend this asset in 2010 into a company called Pharmasafe. See the 11 October 2010 market release from GoConnect (ASX: GCN), a large shareholder of Pharmasafe, headlined *'Agreement to merge Pharmasafe with NGPDT Asia Pacific and listing of expanded Pharmasafe on ASX'*. This transaction failed to proceed.
[2] Invion issued 2.75 billion ordinary shares at 0.2 cents per share, which was the price at which Invion stock had last traded prior to the 31 August announcement. Previously there had been 1.46 billion shares on issue.
[3] New shares from this rights issue commenced trading on 16 March 2018.

Invion has spun off its old drug development assets

of IVX-P02 in various cancers, ahead of potential Australian and New Zealand registration, possibly in 2021.

Why did Invion change direction so that it is now focused on PDT? Between 2012 and 2016 Invion worked primarily on the repurposing of an old blood pressure drug called nadolol while before then, from 2010 to 2012, when it was known as CBio Ltd[4], it had been working on a new biological anti-inflammatory drug called XToll. By 2016 Invion had evidence that nadolol's capability as a beta-2 adrenergic inverse agonist would make it useful in a range of respiratory disease conditions, most notably asthma, chronic bronchitis and smoking cessation. Significantly, the company had participated in an end-of-Phase 2 meeting with the FDA regarding nadolol's use in patients with COPD where those patients could not quit cigarette smoking. Despite this clinical progress, Invion faced difficulties raising the necessary capital to move to Phase 3 with nadolol. This caused the company to look for other biomedical opportunities while seeking to out-license the nadolol programme, and that search culminated in the NGPDT Transaction. In September 2018 Invion announced that some of the original Invion assets would be spun out into a new company called Chronic Airway Therapeutics Ltd, with that company to raise fresh venture capital. The shares of Chronic Airway Therapeutics were subsequently distributed *pari passu* to Invion shareholders.

Why is Invion currently capitalised at A$71.5m when it is still pre-clinical with IVX-PO2? Invion stock re-rated strongly after completion of the NGPDT Transaction, in part because of the removal of funding risk from the story. The stock has since come back; however, we see potential for the stock to re-rate again as the clinical development of IVX-P02 further de-risks this product.

Nine reasons to look at Invion

1. **Invion's Photodynamic Therapy is part of an emerging treatment paradigm for cancer**, with the in-licensed Photosoft technology having shown, in various case studies and early clinical studies, that it can potentially treat a range of cancers.
2. **Invion's new formulation of Photosoft, called IVX-P02, shows promise across a range of cancers**, with the company pursuing early approvals in non-melanoma skin cancer and actinic ketatosis, to be followed by indications in various solid tumours.
3. **Tookad's clinical success can help to mainstream Photodynamic Therapy.** The 2016 Phase 3 clinical success in prostate cancer, and November 2017 European approval, of Steba's Tookad PDT has the potential to moves PDT into the mainstream, allowing competitor products with the right drug properties, such as IVX-PO2, to emerge.
4. **Invion may have a valuable new treatment option for localised prostate cancer.** In recent years men with localised prostate cancer have increasingly preferred 'watch and wait' to potentially damaging surgery or radiotherapy. Photodynamic Therapies like Invion's represent a valuable alternative given the safely profile.
5. **Invion's product may work well with cancer immunotherapy**, with a proteomics analysis of proteins found in the urine of patients showing various immune-related biomarkers.

[4] CBio (ASX: CPZ), first listed on the ASX in February 2010 after an IPO at $1.00 per share raised $7.1m. The company had originally hoped to raise A$30m at $1.00 each

6. **Invion's speed to market is relatively high**. We argue that the company can be looking at its first regulatory approval in Australia for basal cell carcinoma and actinic keratosis by around 2021.
7. **Invion's clinical programme does not have funding risk**. With the costs of the development and clinical trials of IVX-P02, being funded via an R&D services Agreement between Invion and the Cho Group, the capital that was raised in the 2018 rights issue is likely to be the last that Invion has to make.

Invion has experienced management

8. **Invion has experienced management**, with CEO Dr Greg Collier having previously built the cancer drug developer Chemgenex prior to its 2011 acquisition by Cephalon.
9. **Invion has potential to re-rate with further clinical development**. We value Invion at 3.1 cents per share base case and 9.8 cents optimistic case using a probability weighted DCF approach. We see Invion re-rating as the clinical development of IVX-PO2 further de-risks this product.

Invion is now a player in Photodynamic Therapy

What is Photodynamic Therapy? Photodynamic Therapy (PDT) is simply the use of light (Greek 'photos') to destroy cancerous or other abnormal tissue. In PDT for cancer, a drug called a 'photosensitising agent' is administered to the patient, which is preferentially taken up by cancer cells[5]. When the patient is exposed to light beams at a wavelength corresponding to the absorption band of the photosensitiser, the drug produces 'reactive oxygen species'[6] that kill nearby cells[7]. As well as direct tumour cell death, PDT works by occluding the blood vessels feeding the tumour[8], and by the induction of an anti-cancer immune response[9]. The science behind PDT has been evolving for over a century, initially for skin diseases[10], and researchers have had clinical evidence since the mid-to-late 1970s of PDT's potential effectiveness in cancer[11]. The PDT field began to mainstream around 1995 when a photosensitiser called Photofrin, generic name porfimer sodium, gained FDA approval, and in the more than two decades since then various groups have worked on developing more effective and better-tolerated photosensitising agents. Photofrin was part of the first generation of photosensitisers based on a molecule found in the blood called hematoporphyrin[12]. Those photosensitisers tended to stay in the patient's body for too long and not take up the longer wavelengths of light that would increase treatment depth[13]. Second generation photosensitisers mostly based on chlorophyll allowed the use of the longer wavelengths. Third generation photosensitisers are now

[5] There are various reasons advanced as to why, although no-one really knows. One possibility is the 'enhanced permeability and retention effect' in which the leaky blood vessels which feed tumours promote the uptake of all sorts of nanomaterials. Or it could be that there's just a lot of newly synthesised collagen in the neighbourhood that naturally binds to porphyrins. Dougherty et. al. suggest a few ideas in J Natl Cancer Inst. 1998 Jun 17;90(12):889-905.

[6] Reactive oxygen species are a type of free radical in which molecules with an oxygen component have unpaired electrons. A free radical must combine with a complementary molecule to achieve chemical stability. If it bonds with a positively charged molecule, its charge is neutralised. If not, the oxygen component of the free radical can damage cells in the body in a process called oxidative stress.

[7] Specifically, the activated sensitiser produces an activated oxygen species called 'singlet oxygen' that oxidises critical elements of the cancerous cells.

[8] Cancer Res. 1999 Sep 1;59(17):4334-42.

[9] See World J Immunol. 2014 Mar 27;4(1):1-11 and Nat Rev Cancer. 2006 Jul;6(7):535-45.

[10] In 1903 Hermann von Tappeiner (1847-1927), Professor of Pharmacology at the University of Munich, working with a local dermatologist called Albert Jesionek (1870-1935), painted a dye called eosin onto a patient's basal cell carcinoma lesion and illuminated it with light (Isr J Chem. Author manuscript; available in PMC 2013 Sep 1). 1903 was also the year that the Dane, Niels Ryberg Finsen (1860-1904), won the Nobel Prize for Physiology or Medicine for showing that the skin disease lupus vulgaris could be treated with concentrated light radiation. In the mid-1950s nurses in England figured out neonatal jaundice could be treated with exposure to sunlight (J Perinatol. 2001 Dec;21 Suppl 1:S93-7; discussion S104-7).

[11] This was demonstrated by the modern PDT pioneer Thomas Dougherty at the Roswell Park Cancer Institute in Buffalo, NY- see J Natl Cancer Inst. 1975 Jul;55(1):115-21 and Cancer Res. 1978 Aug;38(8):2628-35.

[12] The discovery of the porphyrins as potent photosensitisers was made in the early 20th Century. In 1912 the German doctor Friedrich Meyer-Betz injected himself with hematoporphyrins to determine their photodynamic impact. After exposure to the sun he experienced the painful photosensitive effect experienced by people with porphyria.

[13] In PDT, the higher the wavelength, the deeper the penetration – see, for a good example, Photochem Photobiol. 1995 Nov;62(5):882-6.

being developed by various academic groups designed to better target the photosensitiser to tumour tissue with, say, the use of conjugated monoclonal antibodies[14].

PDT can be performed quickly on an outpatient basis

Why Photodynamic Therapy can potentially be a valuable treatment option for cancer patients. There are number of obvious theoretical advantages to treating cancer with PDT:

- PDT can be targeted very precisely, thereby avoiding the usual side effects of systemic treatment;
- PDT can be used to debulk difficult-to-reach tumours prior to surgery;
- PDT is minimally invasive, in that the light source used can often be applied externally;
- PDT is repeatable, unlike many radiation therapies;
- PDT is low cost;
- PDT can be performed quickly on an outpatient basis.

If Photodynamic Therapy is so good, how come it's not routine in cancer therapy yet? Often in the history of cancer therapy various treatments are discovered, then largely ignored by the mainstream for decades before being taken up again. A classic case is cancer immunotherapy, where the patient's own immune system is harnessed to attack the cancer. This approach was first worked on in the 1890s[15] but its clinical potential is only being realised today[16]. Generally, the catalyst for the rediscovery of the forgotten approach is one successful clinical study of a new agent after a long history of products that showed promise but had drawbacks of some kind. This is indeed PDT's history. Since Photofrin, better photosensitisers have been developed, but none has quite got to the point where it is a must-use therapy for any cancer. 5-Aminolaevulinic acid (5-ALA), a porphyrin pro-drug, worked faster than Photofrin but had poor bioavailability[17]; Metvix and Hexvix[18], esters of ALA, had better bioavailability but were weak on long-wavelength absorption and so remained largely for diagnostic use only. Foscan (temoporfin) proved useful therapeutically, and as a result gained European approval in 2001 for the treatment of head and neck cancer[19], because as a chlorophyll derivative it had improved long-wavelength absorption, however the product was not water soluble and for that reason probably had poor tissue distribution which left patients photosensitive for around three weeks after initial illumination. As we'll see below, it has taken until the Phase 3 data from a new product called Tookad for three key issues with PDT to be satisfied:

- Water solubility for good tissue distribution that allows ideal targeting to tumour sites[20].
- Strong absorption of long wavelengths allowing cancer to be reached at depth;
- Low circulation times so that patients aren't left vulnerable to damage from sunlight.

[14] Br J Pharmacol. 2008 May; 154(1): 1–3.
[15] The American surgeon William Coley (1862-1936) helped sarcoma patient John Ficken to live another 26 years with 'Coley's toxins', first administered to him in 1893 -see Ann Thorac Surg. 1999 Sep;68(3 Suppl):S28-33.
[16] Another example is brachytherapy, where radioactive beads are placed at the site of the tumour for localised radiotherapy. This was tried out by the British surgeon Sir Geoffrey Keynes (1887-1982) in the late 1920s. Brachytherapy, however, really became feasible in the 1990s when imaging modalities allowed better positioning of brachytherapy.
[17] J Pharmacol Exp Ther. 2002 May;301(2):507-12.
[18] Developed by the Norwegian biotech company Photocure (Oslo, OSE: PHO, www.photocure.com). See www.hexvix.com.
[19] It is still marketed by the German company biolitec – see www.biolitecpharma.com.
[20] Trends Biotechnol. 2008;26:612–621.

We argue that, with Tookad approved in Europe, PDT is set to mainstream in cancer therapy. Invion expects to benefit from Tookad's success as interest in PDT by oncologists increases globally and the Australian company and its Chinese partner comes forward with a competing product.

What is Next Generation Photodynamic Therapy? NGPDT, also called Photosoft E4 or just plain Photosoft, is a chlorophyll-based PDT photosensitiser that was developed by the Cho Group around a decade ago. Specifically, it is a complex of chlorin, chlorophyllin and zinc[21] which activates at three light wave sensitivity ranges - 430 nm, 630-650 nm and the Near-Infrared (NIR) wavelength range of 750-850 nm. The latter range is particularly important as it allows good body penetration for the light source, and, potentially, the ability to hit Circulating Tumour Cells[22]. The chemistry of Photosoft is water soluble, and the product's bioavailability is so good it can be administered sublingually rather than intravenously as needed, allowing for patient convenience when appropriate. The Cho Group regularly administers Photosoft to patients in a clinic in Guangzhou[23].

NGPDT has worked well in case studies

What clinical work has been performed with NGPDT/Photosoft? The Cho Group and others have reported case and clinical studies of NGPDT/Photosoft in various cancer settings.

- **Case studies**. In China patients have been treated at the Cho Group's clinics for some years now. We have identified one online anecdotal report from an Australian patient treated for cervical cancer in late 2013[24], and the Cho Group have logged several encouraging case studies on the NGPDT web site[25] featuring patients with nasopharyngeal carcinoma, astrocytoma (a brain cancer), neurinoma of the peritoneum (a cancer of the peripheral nerves in the membrane lining the abdominal cavity), and lung cancer. There are also several case reports on the Cho Group's WO/2014/091241 patent application. An online search shows increasing patient interest in NGPDT[26] but also concern at the lack of data on effectiveness as far as randomised controlled trials are concerned[27]. This is Invion's opportunity to make Photosoft more 'respectable' with larger, carefully designed clinical studies[28].
- **An initial Australian Phase 1 in prostate cancer, 2013.** The Geelong urologist Dr Donald Murphy and collaborators administered Photosoft to 68 prostate cancer patients. Results for 26 patients that had been treated for >6 months were reported at the Urological Society of Australia and New Zealand meeting in Melbourne in April 2013. Murphy found half of these patients had stable to decreasing PSA and half increasing PSA, while prostate size was generally falling on assessment using diagnostic imaging[29].
- **A second Phase 1 in prostate cancer, 2017.** A second Phase 1 has been completed by Donald Murphy in collaboration with Monash University, and a paper has been prepared for publication. This study evaluated 36 patients, 23 with localised treatment-naïve prostate cancer and 13 with

[21] The chlorin and chlorophyllin used are Chlorin-e6 and Chlorophyllin-A - see WO/2014/091241, priority date 14 December 2012.
[22] That is, the cells that cause cancer metastasis through the circulatory system - see PLoS One. 2015 May 26;10(5):e0127219.
[23] We understand the approval of the product in China was as an oral version of Photosoft as basically an OTC drink.
[24] http://cancertreatmentstory.com.au/integrated-cancer-treatment/ngpdt.
[25] www.nextgenerationpdt.com.
[26] See, for instance, the report from a Perth-based patient named Jim Corby at www.dadscure.com/cancer-treatment-plan-considering-ngpdt.
[27] See, for example an article in *The Guardian* from 30 November 2012 by Sarah Boseley headlined '*Cancer patients warned against clinics offering unproven treatments*'. This article mentions a warning on NHS Choices regarding NGPDT.
[28] This is particularly important in the light of the 2016 discovery by the China Food and Drug Administration of potentially fabricated data related to products that are approved in that country - see *CFDA disputes claim that 80% of Chinese trials faked data but admits serious problems* by Phil Taylor, FiercePharma, 24 October 2016.
[29] See www.nextgenerationpdt.com/clinical-studies/clinical-study-prostate-cancer-treated-by-ngpdt.

local relapse. In the study Murphy was evaluating another photosensitiser called Radachlorin and a 'sonosensitising agent' called SF1[30] as well as Photosoft, so for the Photosoft patients there were only 22 evaluable patients.

What do we know about the effectiveness of Photosoft? The 2017 Murphy et. al. study showed that Photosoft was safe and well-tolerated[31]. As for efficacy, the investigators checked the PSA levels of NGPDT-treated patients at three months post-treatment and found 10 of 15 first-line patients registering stable PSA, but only one of seven PSA-stable in the relapse group. However, these patients had their sensitising agent activated by both light and sound. For the light-only Photosoft group, the comparable figures are 4 of 7 first line patients and none of three relapse patients. This suggests the potential for efficacy in a first-line setting, but a larger Phase 2 study, probably of 50-100 patients, using just Photosoft, would be needed before stronger confidence can be placed on treatment outcomes. That said, there were two encouraging aspects of this study:

- **Reduced prostate size**: Murphy et. al., while not going into details, report a 'serendipitous finding of a global reduction in prostatic size was noted across the primary treatment group'.
- **An apparent anti-cancer immune response**. Scientists from Melbourne's Hudson Institute of Medical Research led by Dr Andrew Stephens did a proteomics analysis of protein samples found in the urine of the patients and found various immune-related biomarkers were upregulated, with high statistical significance ($p<0.001$). Andrew Stephens joined Invion's Scientific Advisory Board in March 2018.

NGPDT can generate an anti-cancer immune response

Immune response – a key potential competitive advantage for NGPDT. Invion believes that the immune response observed by Murphy et. al. in the Phase 1 give it a potential advantage over other water-soluble PDT therapies such as the aforementioned Tookad, now being brought to market by Steba Biotech, a privately-held company based in Luxembourg[32]. There is a growing body of knowledge that PDT has the potential to generate an anti-cancer immune response[33], which, in the era of immuno-oncology we have moved into with BMS's Yervoy in 2011 and Merck & Co.'s Keytruda in 2014, is likely to attract a lot of attention from oncologists and researchers alike.

Tookad's Phase 3 in prostate cancer has potential to take PDT well and truly into the mainstream. Tookad, generic name padeliporfin, is a new photosensitising agent derived from the bacteriochlorophyll found in aquatic bacteria. The product was originally developed at the Weizmann Institute in Israel[34] and then licensed to Steba, which completed a successful Phase 3 in prostate cancer in early 2016 and gained European approval in November 2017. We argue that Tookad can take PDT well and truly into the mainstream[35]:

- Unlike most photosensitisers investigated to date, Tookad is water soluble, and, encouragingly, the product activates at a NIR wavelength of 753 nm, which, as we noted above, allows great depth penetration. Also, the product acts via the vascular occlusion mechanism rather than

[30] Sonodynamic Therapy (SDT) is like Photodynamic Therapy, only ultrasound rather than light is used to activate the relevant drug – see Integr Cancer Ther. 2008 Jun;7(2):96-102.
[31] See Invion's February 2018 Corporate Presentation, slide 20.
[32] See www.stebabiotech.com.
[33] See, for example, Int J Biol Sci. 2016; 12(1): 120–132.
[34] Photochem Photobiol. 2005 Jul-Aug;81(4):983-93.
[35] PDT was first tried out in prostate cancer on two patients in 1990 by Windahl et al. at Orebro Medical Centre in Sweden tried out Photofrin and seemed to work well (see Lancet. 1990 Nov 3;336(8723):1139) however this work was never followed up. Moore et. al at University College London tried out at photosensitiser called mTHPC in interstitial prostate cancer, again with some success, in 2006 (Lasers Surg Med. 2006 Jun;38(5):356-63).

directly on the tumour cells, so that the damage to healthy tissue is minimised.

- Tookad's 413-patient randomised controlled Phase 3 in low-risk prostate cancer, which compared the product 1:1 with 'active surveillance'[36], saw the Tookad group register a 28% progress rate at 24 months versus 58% for active surveillance ($p<0.0001$). Also, at 24 months 49% of the Tookad group had a negative prostate biopsy as against only 14% for active surveillance ($p<0.0001$). This data, for which top line results became available in January 2016, were published in *The Lancet Oncology* in December 2016[37].
- The reason that active surveillance is an accepted treatment option for most low-risk prostate cancer is that, as we'll see below, the potential side effects for surgery and radiotherapy are considered too high for many patients and their treating physicians. In the US, this has led to a trend where up to half of all patients choose active surveillance[38]. New, low-cost therapies with Tookad are reasonably expected to tap this considerable opportunity.

The path to market for Invion with PDT involves multiple cancer therapies

Photosoft is likely to be useful across a range of cancers

Photosoft is likely to be useful across a range of cancers. While Invion largely talked of the prostate cancer opportunity around the time of the NGPDT Transaction, by April 2018[39] it was foreshadowing a pipeline of opportunities with its PDT alongside prostate cancer, notably:

- **Skin cancer:** PDT is often used to treat skin cancers such as actinic keratosis or some cases of nodular basal cell carcinoma, which makes sense because the skin is readily accessible to light-based therapies[40]. Invion sees an opportunity to move quickly into this space given the general acceptance of PDT in Australia[41]
- **Ovarian cancer**. In ovarian cancer conventional treatment options are limited but the clinical data from other PDTs is encouraging[42]. Invion reported in July 2018 that IVX-P02 had been found to have high levels of activity in multiple ovarian cancer cell lines *in vitro*. The work on ovarian cancer was presented at Combio, the annual meeting of the Australian Society for Biochemistry and Molecular Biology, in Sydney in September 2018, where Andrew Stephens was able to report that Photosoft performed better than the aforementioned Foscan PDT.

Invion spent 2018 and early 2019 assembling the elements of future clinical success. In preparation for Invion taking Photosoft into the clinic in Australia, it needed to take care of four matters – R&D, product manufacturing, choice of indication, and the right team:

- **R&D** - The company signed a Research and Development Alliance Agreement with the Hudson Institute, which is part of Monash University, in March 2018, with the two parties agreeing to work on various projects related to Photosoft. We expect that Invion's Hudson Institute

[36] That is, biopsy every twelve months, and PSA test and digital rectal exam every three months.
[37] Lancet Oncol. 2017 Feb;18(2):181-191. Epub 2016 Dec 20.
[38] See *More men with early prostate cancer are choosing to avoid treatment* by Gina Kolata, New York Times, 24 May 2016.
[39] See Invion's investor update of 30 April 2018.
[40] Dermatol Clin. 2007 Jan;25(1):5-14.
[41] Australas J Dermatol. 2016 Aug;57(3):167-74. Epub 2015 May 31.
[42] Cancers (Basel). 2016 Oct; 8(10): 88.

collaborators can help the company firm up its clinical development plans.

- **Manufacturing**. Photosoft had been used clinically in China for several years but as part of the process of preparing it for use outside China Invion decided to have the product formulated to GLP standards by an Australian manufacturer. The resulting product, called IVX-P02, was subsequently found to have 15-fold better potency against ovarian cancer cells lines *in vitro* than the original Photosoft, which Invion now calls 'Photosoft Oral'. The work that went into IVX-P02 has also allowed valuable know-how to be gathered as well as formulations suitable for skin conditions to be developed, and Invion was able to unveil an IVX-P02 gel in November 2018.It is currently working on an IV formulation of IVX-P02 for solid tumours.
- **Indications**. During 2018 Invion's leadership had discussions with various clinicians in Australia on the indications to pursue and by the end of the year had settled on non-melanoma skin cancer for its lead programme.
- **The team**. By early 2019 Greg Collier and colleagues had brought together a clinical and regulatory team as well as a group of scientific advisers.

Invion has markedly improved its original PDT formulation

This year Invion takes IVX-P02 into the clinic. By late February 2019 Invion was able to talk in detail about the clinical path for IVX-P02[43]:

- Initial clinical work will see the IVX-P02 gel studied in non-melanoma skin cancer, with a Phase 1 in basal cell carcinoma to be followed by a couple of Phase 3s between now and early 2020.
- Subsequently clinical work with an IVX-P02 intravenous formulation will involve an initial indication in mesothelioma to be followed by potential indications in prostate, ovarian and lung cancer

Invion expects to Initiate Phase 1s in basal cell carcinoma and in mesothelioma in the third quarter of 2019. This puts the company on a path to be filing for its first Australian or New Zealand registration in 2021 for non-melanoma skin cancer and for mesothelioma possibly in 2023.

IVX-P02 in non-melanoma skin cancer

Skin cancer is common, but not all skin cancer is the same. There are three major types of skin cancer: basal cell carcinoma (BCC), squamous cell carcinoma (SCC), and melanoma. BCC and SCC are cancers of the epidermis, the outermost of the three layers that make up the skin[44]. Melanoma is a cancer of the skin's pigment-producing cells, the melanocytes. BCC and SCC can be grouped together as non-melanoma skin cancer (NMSC) and while both cancers are malignant, they are unlikely to metastasise. Melanoma, by contrast, is a highly aggressive and metastasising cancer. The thing about skin cancer is its high frequency in countries with predominantly Caucasian populations. In the US[45], for example, more than 5.4 million cases of nonmelanoma skin cancer were treated in over 3.3 million people in 2012[46].

[43] See the company's 28 February 2019 Corporate Presentation entitled '*Transforming Photodynamic Therapy: for novel & effective treatments for cancer*'.
[44] The basal cells are in the lowest part of the epidermis while the squamous cells are the next level up. Squamous cells are so called because of the 'scaly' look of the cells (Latin squāmōsus, 'scale').
[45] Where the population is 77% white – source: US Census Bureau, United States Population estimates, July 1, 2017.
[46] JAMA Dermatol. 2015 Oct;151(10):1081-6.

This year it is estimated around 190,000 Americans will be diagnosed with melanoma[47].

Australia and New Zealand have high skin cancer incidence rates

Why non-melanoma skin cancer makes a great first indication for IVX-P02. As Australians and New Zealanders well know, their countries have some of the highest skin cancer rates in the world[48], as a result of a predominantly Caucasian population inhabiting areas of the world with a high level of Direct Normal Irradiance. Australia has at least 400,000 new cases of non-melanoma skin cancer per year[49] and around 13,000 new cases of melanoma[50], in a population of only around 25 million. Invion believes it has a new treatment option for the NMSCs, as well as a precancerous condition of the skin called actinic keratosis (AK), where in excess of 600,000 patients are treated each year in Australia[51].

PDT has been used to treat non-melanoma skin cancer for many years. Traditional surgery or, more recently, cryosurgery[52] (involving the use of extreme cold to ablate abnormal tissue) have been the standards of care for NMSC and AK, but generally the results have not been good from a cosmetic point of view. Because the NMSCs tend not to metastasise, and, as we noted above, the skin is readily accessible to light-based therapies, PDTs have in recent years been used more frequently because of the better cosmetic outcomes and the apparent non-inferiority to surgery. Metvix, for example, continues to be marketed by the Nestlé dermatology unit Galderma for NMSC[53], and there are even guidelines for the use of PDT use from the dermatology professional societies[54]. The downside for existing therapies, however, is the pain associated with them[55] as well as general patient tolerance. The evidence for Invion to date is that their PDT would not have pain associated with it.

The path forward for IVX-P02 in NMSC. Invion intends to initiate, in the second half of calendar 2019, a Phase 1 study in BCC patients, to be followed shortly thereafter by Phase 3 studies in BCC (versus Metvix plus traditional surgery) and in AK (versus Metvix plus cryosurgery). The company believes that these studies can be completed in early 2020, allowing it to potentially gain Australian approval by 2021.

IVX-P02 in mesothelioma

Invion is working on its first solid tumour indication

What is mesothelioma? Mesothelioma is a cancer of the mesothelium, that is, the cells of the protective sacs that line the lungs (the pleura) and the abdomen (the peritoneum). It used to be one of those cancers no one had heard about. It's still an uncommon cancer, not fitting, for example, into the list of cancers recorded in the American Cancer Society's Cancer Facts and Figures list. The cancer is, however, not unheard of anymore. Two developments of the 20th Century saw to that. One was the presence in the early polio vaccines of a virus that infects monkeys called SV40. That virus, which was not identified until 1960, five years after the polio vaccine was introduced, was later demonstrated to be able to induce mesothelioma in an

[47] Source: American Cancer Society, Cancer Facts and Figures 2019.
[48] Br J Dermatol. 2009 Nov;161 Suppl 3:116-23.
[49] Source: AIHW, *Non-melanoma skin cancer: general practice consultations, hospitalisation and mortality*, 15 October 2008.
[50] Source: AIHW, *Skin cancer in Australia*, 13 July 2016.
[51] F1000Res. 2014 Aug 5;3:184.
[52] Dermatol Surg. 2004 Feb;30(2 Pt 2):297-300.
[53] J Dermatolog Treat. 2003;14 Suppl 3:15-22.
[54] Consider, for example, the guidelines from the European Academy of Dermatology and Venereology in J Eur Acad Dermatol Venereol. 2013 May;27(5):536-44.
[55] See, for example, Clin Exp Dermatol. 2002 Sep;27(6):493-7 and Photodiagnosis Photodyn Ther. 2017 Sep;19:308-344.

animal model. Which means that polio vaccines administered up until 1961 may have been causing mesothelioma[56]. However, most of the mesothelioma patients now in treatment contracted their condition from something a little more prosaic – their exposure, generally in their daily work, to the mineral asbestos. Workers handling the fibrous material, it is speculated, breathed it into their lungs where it become lodged in the pleura, and then caused irritation that changed the surrounding normal cells into mesothelioma cells. The resultant cancer happened, ominously, after a long latency period. It takes about 30 years for a case of mesothelioma to show up, but the disease then kills its victim with alacrity, the median Overall Survival period post diagnosis being a mere 15 months[57] because of the cancer's usual inoperability and lack of response to radiotherapy. Large-scale asbestos use in industry only really started with the Second World War and the first bans didn't come in until the 1970s, so new cases of the disease are not expected to peak in some countries until the 2020s[58]. And these new cases are coming not just from the men who mined it at places like Wittenoom in Western Australia[59], but from men involved in the building trade, as well as many shipyard workers and people who laboured in appliance factories as well up until the 1980s, in each case because asbestos made a great insulation material due to its resistance to burning as well as its poor showing as a heat conductor. Mesothelioma may be a 'high profile' cancer however the disease still has a relatively small incidence in the industrialized world. In the United States there are only around 2,000 new cases of mesothelioma annually[60] and around 10,000 in other advanced industrial countries[61].

Mesothelioma studies can read out data quickly

Why Invion is pursuing a mesothelioma indication for IVX-P02? The reason that Invion is contemplating an initial study for its IVX-P02 IV formulation is twofold:

- Such studies can gain a read-out data quickly, since even with Eli Lilly's Alimta drug[62], FDA approved in 2004, patients generally only live around three months longer than expected[63].
- Generally, mesothelioma clinical studies can be run in Australia[64].

The path forward for IVX-P02 in mesothelioma. Invion contemplates a Phase 1 study of its IV formulation in healthy volunteers to initiate in the second half of 2019, to be followed by an 18-patient Phase 3 in mesothelioma patients to be run between 2020 and 2022.

IVX-P02 in prostate cancer

Tookad provides a pathway for Invion to follow in prostate cancer with IVX-P02. We believe that the two co-primary endpoints from Tookad's Phase 3 – treatment failure and absence of definite cancer – provide a pathway for Invion to follow with IVX-P02 in prostate cancer. We see the following approach being taken by Invion once it turns its attention to this condition:

[56] Anticancer Res. 1999 May-Jun;19(3B):2173-80.
[57] F1000Res. 2018 Aug 3 [revised 2018 Dec 19];7:1184.
[58] Ann Cardiothorac Surg. 2012 Nov;1(4):491-6.
[59] A town in the Pilbara region of WA around 1,400 km north-north-east of Perth where the asbestos mineral crocidolite was mined in three separate mining stages and locations from 1937 until 1966.
[60] MMWR Morb Mortal Wkly Rep. 2017 Mar 3;66(8):214-218.
[61] See Scand J Work Environ Health. 1997 Aug;23(4):311-6. One group estimated that as many as 43,000 people worldwide die from the disease each year – see Am J Ind Med. 2005 Dec;48(6):419-31.
[62] Generic name pemetrexed, see www.alimta.com
[63] J Clin Oncol. 2003 Jul 15;21(14):2636-44.
[64] Historically the University of Western Australia has been a key research centre globally for the condition. UWA now hosts the National Centre for Asbestos Related Diseases.

- A Phase 2 single arm study recruiting only low-risk treatment-naïve patients with newly diagnosed localised prostate cancer. The study would probably require 50-100 patients and treat those patients only with IVX-P02. We expect that this Phase 2 would see the photosensitiser administered intravenously to improve and speed uptake into cancer cells, as against the sublingual delivery used by the abovementioned Donald Murphy and colleagues, which required a 15 hour wait between the administration of the drug and the application of the light source[65].

Tookad provides the pathway for NGPDT to follow in solid tumours

- A Phase 3 randomised study controlled against active surveillance, probably of 400 patients. This Phase 3 would likely vary from Tookad's approach in using MRI rather than biopsy to measure the endpoints, since the latter approach is non-invasive and speeds up the process of data gathering faster.
- A small proof-of-concept study of perhaps a dozen patients evaluating the potential of IVX-P02 to debulk tumours prior to surgery or radiotherapy. This could be used in preparing larger studies to show that, where these traditional modalities become necessary, PDT can reduce the side effect profile.

Prostate cancer survival rates are high, but there remains opportunity for new therapies. Prostate cancer is, notionally, a large market opportunity. In most Western countries, it is the third most common cancer after breast and lung, and the most common in men. The trouble with prostate cancer as a market for new therapies, as many see it, is that incidence and mortality are declining. The decline in incidence has more to do with a change in diagnostic strategy – the PSA test routinely used in the 1990s was overdiagnosing the disease[66] and is now less relied on. However, the decline in mortality has been a striking example of the success of early diagnosis. In the US five-year survival rates for men, across all stage of cancers, was 68% in the mid-1970s but this had improved to 83% in the late 1980s and to virtually 100% today[67]. When prostate cancer is diagnosed at the local stage it can be managed with relative ease using surgery, radiotherapy, ablative therapy (ie treatment that destroys the tumour without removing it), or active surveillance[68]. However, it is patient dissatisfaction with these modalities that opens up opportunities for approaches like IVX-PO2. Surgery and radiotherapy are radical treatments associated with urinary incontinence (9-18% over 15 years), erectile dysfunction (87-94%) and poor bowel function (22-36%)[69]. Ablative therapies may have a better side effect profile but are not necessarily cost effective[70], and the data on cryotherapy, where erectile dysfunction is commonplace[71], has blunted the popularity of all ablative therapies. No wonder, then, that active surveillance has gone from something like 6% of patients in the US in the early 2000s to over 40% now[72]. Indeed, Donald Murphy became interested in PDT, and ran his studies with NGPDT, because of the increasing number of his patients who didn't want ablative therapy. Given the trend towards non-treatment where possible, we argue that PDT, because it is low cost and non-invasive, has the potential to attract a large following, either as

[65] This would obviously require routine toxicology studies prior to the commencement of the study.
[66] BMC Med. 2014 Feb 11;12:26.
[67] Source: American Cancer Society, Cancer Facts and Figures 2017.
[68] In the US only around 5% of prostate cancer presents where the cancer has metastasized and the five-year survival prospect is only 30% - source: SEER. After cancer has metastasised the treatment options are hormone therapy followed by the now off-patent taxotere, or newer drugs such as Sanofi's Jevtana, J&J's Zytiga and Pfizer's Xtandi. The last-named drug was the reason Pfizer bought Medivation for US$14bn in mid-2016.
[69] N Engl J Med. 2013 Jan 31;368(5):436-45.
[70] Health Technol Assess. 2015 Jul;19(49):1-490.
[71] BJU Int. 2009 Mar;103(6):788-92. Epub 2008 Sep 12.
[72] Nat Rev Urol. 2016 Apr; 13(4): 205–215.

a monotherapy, or by facilitating surgery through pre-operative tumour debulking.

Valuing Invion

We valued the IVX-PO2 opportunity using a probability-weighted DCF approach. We used a 15-year time horizon, valuing the opportunity across the range of indications currently of interest to Invion and assuming Invion would commercialise IVX-P02 by sales of drug to third-party clinics[73]. We assumed that the product could launch in Australia and New Zealand in calendar 2022 (conservative since Invion believes there is potential for first approvals in 2021), after the completion of Phase 3 studies, and adjusted out DCF to account for the probability of clinical success. Figure 1: Key valuation parametersFigure 1 contains our key valuation parameters

Figure 1: Key valuation parameters

	BASE	OPTIMISTIC
Market share by year 15	25%	40%
Initial revenue per patient (A$)	1,200	1,800
Annual price increase	2.0%	3.0%
Initial gross margins	65.0%	75.0%
Gross margins by year 15	75.0%	85.0%
Maximim field force (reps)	20	10
Working capital % of sales	25.0%	18.0%
Terminal growth rate	3.0%	3.0%
Terminal EBITDA margins	35.0%	50.0%

Source: Pitt Street Research

We gave Photosoft a 20% chance of success

Chances of success roughly one in five. When valuing any investigational new agent, it is necessary to apply a probability weighting to account for the chance of either clinical failure or the unwillingness of regulators to approve the product. Drug development is risky, and many drug candidates fail either at pre-clinical, in the various clinical stages of development (Phase I, II and III), or at the regulatory stage when agencies have to make the decision to approve or not-approve a drug. For clinical stage drug candidates, there are databases available[74] stretching back to the 1960s that have allowed researchers to estimate the probability of success at various stages of development. One recent estimate is shown in Figure 2. Multiplying the probabilities in each case suggests that the probability that a drug entering Phase 2 will ultimately gain regulatory approval is around 21% for small molecules. Since IVX-PO2 is a small molecule, we have used this probability weighting for both our base and optimistic case.

Cost of capital. A key question in developing a DCF model is the cost of capital. We used we use the following approach:

[73] That is, instead of starting its own clinics, as the Cho Group have done.
[74] Most notable from the Center for the Study of Drug Development at Tufts University in Medford, Ma. (see csdd.tufts.edu).

- **Risk-Free Rate**. We use the Australian Ten-Year Bond Rate, which is currently 1.6%;

Figure 2: Probabilities of clinical success

	SMALL MOLECULES	LARGE MOLECULES
Phase I	63%	84%
Phase II	38%	53%
Phase III	61%	74%
Filing for approval	91%	96%
Phase I to approval	13%	32%

Source: Clin Pharmacol Ther. 2010 Mar;87(3):272-7. Epub 2010 Feb 3.

- **Market Risk Premia**. We use three basic MRPs for Life Science companies - 7.5% for 'medium risk' companies[75], 9.5% for 'high risk' companies and 11.5% for 'speculative' companies. We regard Life Science companies with existing businesses, or who have enough capital to reach the market with their products, as 'Medium' risk. Companies that have small revenue streams from marketed products but that are still potentially in need of capital are 'High' risk. Everything else is 'Speculative'. We regard Invion as 'Medium Risk', since global development of IVX-PO2 is being funded via an R&D services agreement between Invion and the Cho Group.
- **Ungeared beta.** We use an ungeared beta of 1.1.

This approach suggests a discount rate for Invion of 10.1% at the present time.

NGPDT's priority date was in December 2012

Commercial life of IVX-P02. We assume that IVX-P02 in Australia and New Zealand enjoys 15 years of commercial exclusivity, partly through WO/2014/091241 (priority date 14 December 2012) and partly through other IP protection that Invion and the Cho Group could be expected put in place around, say, mechanisms of action for the IVX-P02 formulation. We assume that the business continues after that, hence our use of a terminal growth rate, but that costs are higher to compete against newer modalities, hence the 25% terminal EBITDA margin.

Royalty to Cho Group. We assume no royalty back to Cho Group, with that company benefiting from the success of NGPDT through its equity stake in Invion.

Patients. We assume that across Australia and New Zealand in 2022 there will be >1,000,000 cases of the NMSCs plus AK as well as prostate, lung and ovarian cancers that would be amenable to IVX-P02 treatment.

Market share at year 15. We believe our assumptions on the caseload by Year 15 is reasonable, since generally, in medicine, a new therapy with no notable competitors can take 80-90% of the addressable market within three to ten years[76].

Pricing and gross margins. We assume that the IVX-P02 gel could enjoy pricing in the order of A$600 per patient while the IVX-P02 IV product could sell for more like A$18,000. We believe our pricing and cost of goods assumptions are reasonable. Consider that for BCC and SCC the total treatment cost in Australia for surgical excisions is in the order of A$1,100 per

[75] We assume that 'low risk' in the Life Sciences industry in Australia and New Zealand does not yet exist for most companies given the formative nature of the industry today.
[76] See, for example, Psychiatr Serv. 2013 Apr 1;64(4):324-30 (related to anti-psychotic medication); Med Care. 2012 Jan;50(1):1-9 (drug-eluting stends); and Am J Manag Care. 2016 Jun 1;22(6):e224-32 (Hepatitis C drugs).

patient[77]. Consider also that for prostate cancer, A$18,000 would fall well within the cost of a radical prostatectomy in Australia, which averaged A$21,500 in 2016[78], as well as the out-of-pockets typically reported by patients[79]. As for gross margins, typically in the pharmaceutical industry these are close to 70%[80].

Overhead costs. EBITDA margin in the pharmaceutical industry is ~20%[81]. This suggests that overhead costs around roughly 50% of revenues. We have used 20-25% since we believe that this level of overhead funds a sufficiently-sized field force – 2 or 3 sales people at the beginning – to adequately grow the business[82].

Working capital. In 2015 pharma companies at the median were investing 18-27% of their sales in working capital[83].

Terminal growth rate. Our terminal growth rate assumptions sit at or below the recent annualised growth in real overall healthcare outlays in Australia[84].

Invion does not have funding risk

Further capital. We assume no further capital needs to be raised given Cho Group has committed to non-dilutive funding for the Australia / New Zealand studies of IVXPO2. We assume that A$50m is contributed in this way over the next few years

Tax losses and corporate overhead. We assume that the company can realise, over time, the value of the $143m in accumulate tax losses. We also assume A$0.15m per month in corporate overhead.

Valuing Invion. Plugging the above assumptions into our model yields a valuation for Invion of base case 3.1 cents per share, optimistic case 9.8 cents per share.

Figure 3: Our valuation of Invion

	Base	Optim.
Value of Photosoft	89.2	479.6
Value of tax losses	44.8	44.8
Corporate overhead	-12.7	-12.7
Cash now (A$m)	0.5	0.5
Cash to be raised (A$m)	50.0	50.0
Option exercises (A$m)	11.0	11.0
Total value (A$m)	182.7	573.1
Total diluted shares (million)	5,865.3	5,865.3
Value per share	$0.031	$0.098
Valuation midpoint	$0.065	
Share price now (A$ per share)	$0.015	
Upside to midpoint	330.0%	

Source: Pitt Street Research.

[77] See the QIMR Berghofer work of Louisa Gordon in a presentation headlined '*Health economics of skin cancer',* slide 6. This presentation was given to the Sunscreen Summit QIMRB on 19 March 2018

[78] Source: Medibank and Royal Australian College of Surgeons*, Surgical Variance Report – Urology*, 2016.

[79] Eur J Cancer Care (Engl). 2017 Jan; 26(1): e12392. The A$4,000 cost differential between open and robot-assisted radical prostatectomy (ANZ J Surg. 2014 Jun;84(6):477-80. Epub 2013 Feb 6.) suggests that A$9,000 could work since it might lower the overall cost of less expensive open surgery.

[80] See *Pharm Exec's 16th Annual Industry Audit* by Bill Trombetta, Pharmaceutical Executive, 22 September 2017, Table 4.

[81] See *Pharm Exec's 16th Annual Industry Audit* by Bill Trombetta, Pharmaceutical Executive, 22 September 2017, Table 5.

[82] Assuming A$200,000 p.a. per sales person.

[83] See *Excess Working Capital has risen 24% to €51 Billion in 2 years*, Informita Pharmaceutical Industry Analysis, April 2016.

[84] Source: AIHW, Australia's health 2016.

Looking forward for Invion

We see a number of events helping to, at the very least, maintain Invion's share price over the next 12-18 months:

- The publication of various papers generated by clinical and pre-clinical work on Photosoft/IVX-PO2;
- Initiation of further clinical studies of IVX-P02 in Australia;
- Publication of further data on the clinical effectiveness of Tookad and other emerging PDTs.

Invion has seasoned leadership

Greg Collier's previous success was Chemgenex

CEO Dr Greg Collier has a track record of success in Life Sciences. Greg Collier made his name on the Australian Life Sciences scene building ChemGenex Pharmaceuticals. Formerly a Professor at Deakin University with a research focus on metabolism, Collier and some colleagues formed a spinout genomics venture around 1998 called Autogen, working on new obesity and Type 2 diabetes therapies. By 2004 Collier's company had evolved into Chemgenex, a drug developer whose lead product, Omacetaxine mepesuccinate[85], had shown activity in patients with both Acute and Chronic Myeloid Leukemias. Over the next seven years Chemgenex took Omacetaxine through to Phase 3 in Chronic Myeloid Leukemia and to a filing for FDA approval before it was acquired by the US specialty pharma company Cephalon for A$230m. Branded Synribo[86], Omacetaxine gained accelerated approval from the FDA only one year after Chemgenex was sold. Not everything Collier has tried has worked out – witness the road blocks into which the nadolol programme has run – but, frankly, that's the Life Sciences industry. We think that the rollercoaster ride of Chemgenex and Omacetaxine has given Collier considerable insights into the cancer drug development process that Invion can now harness with IVX-P02.

The Invion board has the skills necessary to building an early stage Life Sciences venture. As well as Collier and his fellow Chemgenex veteran **Dr James Campbell** (now CEO of the antibody drug developer Patrys[87]), the Invion board also has the company's new Chairman **Thian Chew** and non-executive director **Alan Yamashita**. Chew, Managing Partner of the Hong Kong investment and consulting firm Polar Ventures, brings financial and technology evaluation skills. Yamashita, another Managing Partner at Polar Ventures, has a financial markets and investment background gained at firms such as Goldman Sachs, Merrill Lynch and Mizuho Financial.

[85] The original natural product was 'homoharringtonine', so called because it came from the bark of a tree native to China whose scientific name was *Cephalotaxus harringtonii*. It was a semisynthetic highly purified homoharringtonine compound that worked by impacting protein synthesis – for background on the drug see Clin Cancer Res. 2014 Apr 1;20(7):1735-40. Epub 2014 Feb 5.

[86] Generic name omacetaxine mepesuccinate, see www.synribo.com.

[87] Campbell was Chemgenex's Chief Operating Officer. Patrys (Melbourne, Australia, ASX: PAB, www.patrys.com).

Appendix I – Chronic Airway Therapeutics and the Original Invion Assets

Invion was historically a drug reprofiler

Invion has historically worked on three pharmaceutical products – INV102 (nadolol in respiratory diseases), INV104 (inhaled zafirlukast for asthma) and INV103 (ala-CPN10 for various inflammatory disorders). INV103 was originally developed by CBio while INV102 was brought into the group when CBio merged with a US company called Inverseon in 2012 and changed its name to Invion. INV104 was in-licensed by Invion in late 2013.

Two of these products have now spun off into Chronic Airway Therapeutics. Invion announced in September 2018 that INV102 and INV104 would be spun out into a new public unlisted company called Chronic Airway Therapeutics Ltd, with that company to raise fresh venture capital. Invion's shareholders voted on this at the company's Annual General Meeting on 13 November 2018, after which the shares of Chronic Airway Therapeutics were distributed *pari passu* to Invion shareholders.

INV102 is a potential new drug for asthma, smoking cessation and other respiratory disorders. This programme originates from work done by Professor Richard Bond of the University of Houston showing that nadolol, an old blood pressure drug, could be an effective treatment option for a range of respiratory conditions including asthma, COPD and cystic fibrosis. The BMS precursor company Squibb[88] had gained FDA approval for nadolol in 1979 under the brand name Corgard, indicated for the treatment of hypertension and angina. The drug was part of a class that had emerged in the 1960s[89] known as 'beta blockers', or, more specifically, 'beta adrenoceptor antagonists', that work because they block the cellular receptors which allow adrenaline to make the heart to beat faster. The thing about nadolol is that it is a 'non-selective' antagonist, meaning that it can inhibit both the beta1 receptors located chiefly in cardiac muscle and the beta2 receptors in the bronchial and vascular muscles. Traditionally, the use of beta2 antagonists was 'contra-indicated' (ie not allowed) in patients with both cardiovascular and respiratory issues, on the assumption the last thing you would want in a patient prone to bronchoconstriction (ie tightening of the airways due to 'hyperresponsiveness' to something that was inhaled) is a drug that would notionally prevent adrenaline from re-opening the airways. Bond argued that, in fact, adrenaline and its fellow neurotransmitters were part of the problem in asthma and other diseases, and, so long as the dose of the beta blocker was titrated up, it would help settle the lungs down. Medicine had already figured this out in heart failure[90], and that realisation had turned a beta blocker called Coreg, from GSK and Roche, into a blockbuster, after its 1997 FDA approval for use in heart failure patients[91]. Bond argued that a similar revolution could take place in respiratory medicine once nadolol could be shown to be effective in this setting. Over the years Bond et. al. gathered significant *in vivo* data to prove his ideas[92], showing that nadolol would reverse mucus metaplasia[93] in the airway epithelium[94], and he even demonstrated a

[88] Bristol-Myers and Squibb merged in 1989 to become Bristol-Myers Squibb.
[89] And won the Scotsman Sir James Black (1924-1910) the Nobel Prize in Physiology or Medicine in 1988.
[90] Basic Res Cardiol. 2000;95 Suppl 1:I15-24.
[91] The drug had originally been developed by the German drug company Boehringer Mannheim, acquired by Roche in 1997. SmithKline Beecham took the US rights. Coreg's original FDA approval for hypertension was in 1995.
[92] See, for example, Proc Natl Acad Sci U S A. 2004 Apr 6;101(14):4948-53.
[93] The appearance of mucus cells in airways where such cells are not ordinarily present.
[94] Am J Respir Cell Mol Biol. 2008 Mar;38(3):256-62. Epub 2007 Dec 20.

mechanism of action that involved the beta arrestin pathway[95]. Bond and his colleagues staked out IP protection around the use of nadolol in this setting[96] and in 2004 they formed a company called Inverseon to develop it. Invion acquired this company in 2012, by which time it had initiated Phase 2 studies in mild asthma and in COPD patients undergoing a smoking cessation programme[97]. The latter study completed in October 2015 with favourable data, leading to an End-of-Phase 2 meeting with the FDA in April 2016. Meantime Invion had started collaborating with 3M Drug Delivery Systems in February 2014 on an inhaled version of nadolol, with potential for high efficacy due to direct delivery of the drug. Invion envisaged that this formulation could potentially be used in cystic fibrosis as well as asthma and COPD.

Invion reckoned it had a better version of zafirlukast

INV104 is a potential new asthma drug. This product is simply a new version an old asthma drug called Accolate, generic name zafirlukast, for which the AZ precursor Zeneca[98] gained FDA approval in 1996. Accolate was a step forward in the treatment of asthma because it was an oral drug that blocked the receptors used by key inflammatory molecules called the leukotrienes. The drug was soon overshadowed by a competitor from Merck & Co. called Singulair (Montelukast) which gained FDA approval in 1998 and was once daily whereas Accolate was twice daily. INV104 originated when Invion's Dr Mitchell Glass, who had been a senior member of Accolate's original development team, figured out that inhaled Accolate could be highly effective at doses as much as 1% of the original oral drug. Invion in-licensed this programme in October 2013 and 3M Drug Delivery Systems started work on the oral delivery system in 2014 at the same time as it took on the inhaled nadolol project. Invion announced in July 2015 that Hovione, the Portuguese contract drug developer and manufacturer[99] would collaborate with Invion on scale-up of the inhaled zafirlukast, to be delivered using a dry-powdered inhaler proprietary to Hovione.

What Invion has achieved with its INV102 programme. Since 2012 Invion has made progress with nadolol/INV102 and has data that would warrant further clinical work should adequate funding be available.

INV102 in smoking cessation. In October 2015 Invion reported favourable results from a Phase 2 of nadolol in COPD patients that were seeking to quit cigarette smoking[100]. Cessation of smoking often temporarily worsens the cough that the ex-smoker has been experiencing, due to improved mucociliary clearance post-cessation[101]. This cough can often hinder efforts to quit. On the expectation that nadolol would help by reducing mucus metaplasia, Invion studied its drug in 121 COPD patients who were on a smoking cessation programme. The investigators found that 19% of patients treated with nadolol had quit smoking at the conclusion of dosing (12 out of 62 patients) versus only 11% for the placebo group (7 out of 59). Where patients had substantially cut back on their cigarette use but not necessarily quit, the comparable figures were 61% for nadolol versus 36% for placebo. This study also confirmed Invion's believe that the action of nadolol on the beta arrestin pathway was what was causing the improved airways, with two biomarkers from that pathway – ERK1 and MUC5AC – reduced in patients

[95] Curr Opin Pharmacol. 2014 Jun;16:50-7. Epub 2014 Mar 27.
[96] See *Methods for treating diseases and conditions with inverse agonists*, WO/2005/034871, priority date 9 October 2003.
[97] See Use of beta-adrenergic inverse agonists for smoking cessation, WO/2012/096866, priority date 10 January 2011, invented by Richard Bond and Mitchell Glass.
[98] Astra and Zeneca Group merged to form AstraZeneca plc in 1999.
[99] Loures, Portugal, privately held, www.hovione.com.
[100] See NCT01825122 at clinicaltrials.gov.
[101] Respirology. 2011 Jul;16(5):849-55.

receiving INV102 compared to placebo. Invion took its data to an End-of-Phase-2 meeting with the FDA in April 2016. We believe this product is Phase 3-ready.

INV102 in mild asthma. Invion completed recruitment of a 66-patient Phase 2 study in chronic asthma patients[102] in November 2015 that was designed to confirm earlier proof of concept work[103]. This study has yet to read out full data. What it did report, however, is interim data showing that while patients were being titrated and after stable dosing for three months there was no requirement to increase rescue medication usage[104].

Inhaled INV102. Invion reported at the 2016 Annual General Meeting that 3M Drug Delivery Systems had been able to manufacture an inhaled formulation of nadolol for toxicology studies, which were underway.

Invion's spin-out can now move to Phase 3

Why Invion formed Chronic Airway Therapeutics. By the time the INV102 data in smoking cessation had come in, Invion's weak share price, at only 1.5 cents per share, meant that the company was only capitalised at $13.4m. The stock failed to rally after this data. That presented difficulties in raising the kind of capital that would be required for further development work on INV102 as well as the other programmes. Since October 2015 Invion had been seeking to partner these programmes but by 2017 it became apparent that funding could be sought from China for these assets in a new company. Hence the formation of Chronic Airway Therapeutics.

Chronic Airway Therapeutics will now go to Phase 3 in China with INV102. China has a serious level of COPD prevalence, with an estimated 14% of all adults over 40 suffering the condition[105] and contributing to a patient population close to 100 million[106]. This has obviously created strong demand for products like INV-102 and Chronic Airway Therapeutics intends to recommence clinical work on that product in China from 2019. Chronic Airway Therapeutics selected a local CRO called R&G Pharma to work on INV102 in September 2018.

INV103, a potential new lupus drug, remains with Invion but will not be developed further. This product was originally developed by Invion's precursor company, CBio, under license from the University of Queensland. INV103, originally called XToll, is a recombinant form of chaperonin 10 or CPN10. The chaperonins are proteins that facilitate the folding of other proteins. The UQ scientists had developed and patented a strong body of knowledge[107] showing that CPN10 had anti-inflammatory properties[108]. CBio's lead indication for CPN10 had been rheumatoid arthritis and it was also working on psoriasis and multiple sclerosis indications. This drug yielded equivocal results in a Phase 2 in rheumatoid arthritis in August 2011 and this ultimately led to CBio acquiring Inversion in order to rebuild shareholder value. Invion, however, continued to work on CPN10, this time as a potential treatment for another autoimmune disorder called Systemic Lupus Erythematosus, over which CBio had IP protection[109]. In August 2015 Invion was able to report evidence from a small Phase 2 study showing that CPN10 could knock down three proinflammatory cytokines highly relevant in lupus - IL-6, TNF-α, and IL-1β. Invion has, however, taken the view that INV103 does

[102] See NCT01804218 at clinicaltrials.gov.
[103] Pulm Pharmacol Ther. 2008;21(1):134-41. Epub 2007 Jul 17.
[104] See Invion's market release dated 23 September 2014 and headlined *'Invion provides update to US FDA on Phase 2 study of nadolol in mild asthma'*.
[105] Lancet Respir Med. 2018 Jun;6(6):421-430. Epub 2018 Apr 9.
[106] Not surprisingly, over half of all Chinese men smoke – see J Epidemiol Community Health. 2017 Feb;71(2):154-161.
[107] See WO/2004/041300, WO/2005/067959, WO/2007/006095, WO/2007/025343, WO/2007/045046, WO/2007/098557, WO/2009/124333, WO/2009/124353 and WO/2011/041847.
[108] Through the inhibition of Toll-like receptor signalling pathways.
[109] See *Prevention and treatment of cutaneous lupus erythematosus*, WO/2011/120076, priority date 30 March 2010.

not warrant further development given the heterogeneity of lupus and the large amount of capital that would be required to go back to the clinic again.

Appendix II - An Invion Glossary

Absorption band – The range of wavelengths in the electromagnetic spectrum that a substance can take up.

Basal Cell Carcinoma (BCC) – A cancer of the basal cells in the lowest part of the epidermis.

Bioavailability – The quantity of a drug that can make it to its target once inside the body. High bioavailability is an important component in a drug's prospects for commercial success. High oral bioavailability is even more desirable because then the drug can be administered in pill form. Some drugs have high bioavailability when injected intravenously but low bioavailability orally.

Biomarker – A natural substance used as an indicator of a biological state, especially to detect the presence or severity of disease.

Chlorophyll – The green pigment in plants necessary for photosynthesis, that is, the conversion of sunlight into fuel.

Debulk – The use of drugs or radiation to reduce the size of a tumour, generally to make it more amenable to surgery.

Epidermis – The outer layer of the skin**.**

Ester – In chemistry, a functional group derived from reacting an alcohol with an acid.

Five-year survival – The probability that a newly diagnosed cancer patient will live another five years.

IV – Short for 'intravenous'.

IVX-P02 – Invion's formulation of Photosoft, developed in 2018.

Mesothelioma – A cancer of the mesothelium, that is, the cells that line the lungs or abdomen. This cancer has its origins in exposure to asbestos fibres.

NGPDT – New Generation Photodynamic Therapy, the PDT product that Invion is leading the global development of, and for which Invion holds the licence and distribution rights in Australia and New Zealand.

NIR – Near Infrared, the region of the electromagnetic spectrum from 750 nm to 2500 nm.

nm – Short for nanometers, the size of an electromagnetic wave.

NMSC – Non-Melanoma Skin Cancer.

Phase – A stage of the clinical trialling process for a drug candidate. Phase I tests for safety. Phase II tests for efficacy in a small sample. Phase III tests for efficacy in a large sample.

Photodynamic Therapy (PDT) – The use of light in the treatment of various diseases, but particularly cancer.

Photosensitiser – A molecule that undergoes a chemical reaction when exposed to light at a certain wavelength.

Photosoft – A trade name for NGPDT

Prostate – The gland in men that produces the seminal fluid that nourishes and transports sperm.

PSA - Prostate-Specific Antigen, a protein produced exclusively by prostate cells often used a a biomarker of prostate cancer.

Radiotherapy – The use of radiation such as X-Rays to attack cancer.

Solid tumour – In cancer, a tumour that is a localised mass of tissue rather than a blood cancer like leukaemia.

Solubility – The ability of a substance to dissolve in another medium. Drugs that are water soluble tend to be easier to delivery orally but drugs that are fat soluble tend to be slightly easier to get the through the cell wall.

Squamous Cell Carcinoma (SCC) – A cancer of the squamous cells in the epidermis.

Systemic – Delivered to the bloodstream rather than to a particular tissue of a clinical trial subject.

Appendix III – Invion's core intellectual property

Invion's intellectual property around NGPDT is covered by a license to one patent family:

Chlorin derivative useful in photodynamic therapy and diagnosis, WO/2014/091241, priority date 14 December 2012, Invented by Honsue Cho.

- This patent application covers the NGPDT complex of chlorin, chlorophyllin and zinc.
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Appendix IV – Invion's capital structure

		% of fully diluted	Note
Ordinary shares, ASX Code IVX (million)	5,500.6	93.8%	
Unlisted options (million)	364.7	6.2%	Average exercise price 3 cents, average expiry date 06-Feb-2023
Fully diluted shares	5,865.3		

Current market cap:	A$82.5 million (US$56.8 million)
Current share price	$0.015
Twelve month range	$0.012 - $0.048
Average turnover per day (last three months)	1.63 million

Appendix V – Major shareholders

Invion currently has only one substantial shareholder:

- **The Cho Group**, a Guangzhou-based investor in a diverse range of ventures, and its associates (66.3%)

Risks related to Invion

Risks specific to Invion. We see five major risks for Invion as a company and as a listed stock:

- **Clinical risk**. There is the risk that the clinical studies of IVX-PO2 sponsored by Invion will miss their primary or secondary endpoints
- **Market acceptance**. There is the risk that IVX-PO2 will fail to attract a strong following from oncologists.
- **Timing risk**. There is the risk that Invion's clinical programme may take longer to executive that the timing we have suggested in this note.
- **Licensing risk.** There is the risk that Cho Group may choose to license its NGPDT technology to groups in other parts of the world, which would impact Invion's potential global market share.
- **Technology risk.** There is the risk that better PDT technologies will emerge over the next five years and progress to market faster.

Risks related to pre-revenue Life Science companies in general.

The stocks of biotechnology and medical device companies without revenue streams from product sales or ongoing service revenue should always be regarded as speculative in character.

Since most biotechnology and medical device companies listed on the Australian Securities Exchange fit this description, the term 'speculative' can reasonably be applied to the entire sector.

The fact that the intellectual property base of most biotechnology and medical device lies in science not generally regarded as accessible to the layman adds further to the riskiness with which the sector ought to be regarded.

Caveat emptor. Investors are advised to be cognisant of the abovementioned specific and general risks before buying any the stock of any biotechnology or medical device stock mentioned on this report, including Invion.

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